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On Pyridopyrazinol Chemistry: Synthesis of Chemiluminescent Substances

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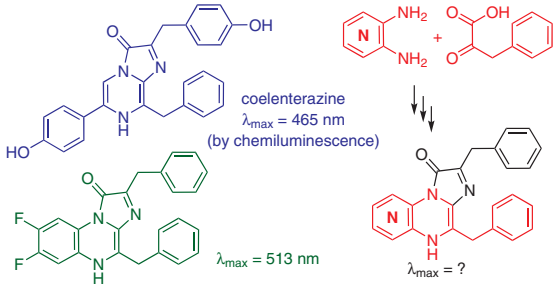

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Abstract Our work on new chemiluminescent substances related to the marine luciferin coelenterazine (λ_{max} = 465 nm) led us to attempt the synthesis of four nitrogen-rich pyridopyrazine-bearing analogues. Accordingly, the preparation of the corresponding benzyl-bearing pyridopyrazinols is studied. By varying the conditions for the condensation of phenylpyruvic acid with 1,2-diaminopyridine or 3,4-diaminopyridine, all the possible pyridopyrazin-2-ol regioisomers are isolated and properly characterized, including by means of crystallographic studies. The ensuing syntheses of the halogenated pyridopyrazines are fraught with difficulties ranging from extensive decomposition to an unexpected ring contraction. In one instance, the inherently reductive mixture of phosphorus oxychloride and phosphorus trichloride provides 2-benzyl-3-chloropyrido[2,3-*b*]pyrazine. This precursor is then transformed into the target *O*-acetylated luciferin (6,8-dibenzylimidazo[1,2-*a*]pyrido[3,2-*e*]pyrazin-9-yl acetate). The 'benzo' derivative of this analogue (i.e., 2,12-dibenzylimidazo[1′,2′:1,6]pyrazino[2,3-c]isoquinolin-3-yl acetate) is also prepared and the chemiluminescence emission spectra of these compounds are determined in a phosphate buffer (λ_{max} = 546 and 462 nm).

Key words chemiluminescence, coelenterazine, imidazo[1,2-*a*]pyrazin-3(7*H*)-one, pyridopyrazine, luciferin, heterocycles, rearrangement

We recently reported on the preparation and chemiluminescence properties of an array of heterocyclic analogues of the luciferin coelenterazine (**1a**), such as compounds **2a**,**b** depicted in Figure 1.[1] Because of their imidazolone component, such heterocyclic systems will, upon an oxidative decarboxylation process, lead to the production of a photon.[1] Similarly, reports have described the synthesis and chemi- or bio-luminescence properties of altered luciferins such as *v*-coelenterazine (**1b**) or the heteroatom-bearing analogues **4**–**6**. In these cases, the structural alterations provided a degree of electron enrichment of the imidazo[1,2-*a*]pyrazine nucleus and, contrary to the blue-hued derivative **3** (λ_{max} = 462 nm), their chemiluminescence emission spectra were shifted toward redder wavelengths.[2] On the other hand, with other types of analogues, we recently achieved a rather modest chemiluminescence shift with a λ_{max} of 513 nm in the case of compound **2b**, which features two electron-attracting fluorine atoms.[1] This result drove us to envisage the synthesis of the four possible aza analogues **7**–**10** in an attempt to study the effect of an additional nitrogen on their chemiluminescence in comparison with compounds **2a**,**b**.

In the event of a tangible red shift of their chemiluminescence spectra, this would pave the way for a research program aimed at an extensive alteration of the catalytic sites of coelenterazine-using luciferases so that these compounds would become actual substrates, and thus provide a red-shifted bioluminescent reporting system. Such an approach has actually been successful in the case of a firefly-based luciferin/luciferase bioluminescence system.[3] Accordingly, we focused on the preparation of the four halogenated pyridopyrazines **11**–**14** which, as we have demonstrated in other instances, are good intermediates for construction of the imidazole component of imidazo[1,2-*a*]pyrazin-3(7*H*)-ones as well as many related heterocyclic systems.[1,4]

Synthetic access to the chloropyridopyrazines **11** and **12** was sought via chlorination of the corresponding isomeric 2-benzylpyrido[3,4-*b*]pyrazin-3-ol (**17**) and 3-benzylpyrido[3,4-*b*]pyrazin-2-ol (**20**). As depicted in Scheme 1, to prepare these substances, we started from two reports describing

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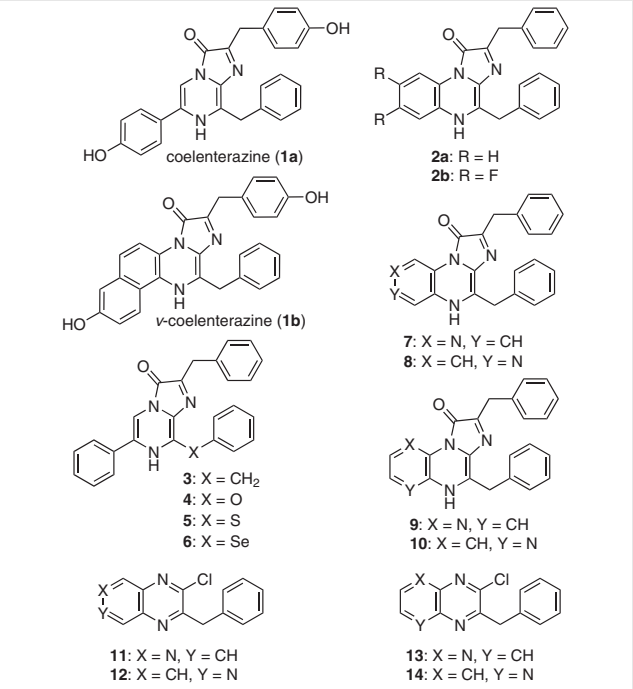
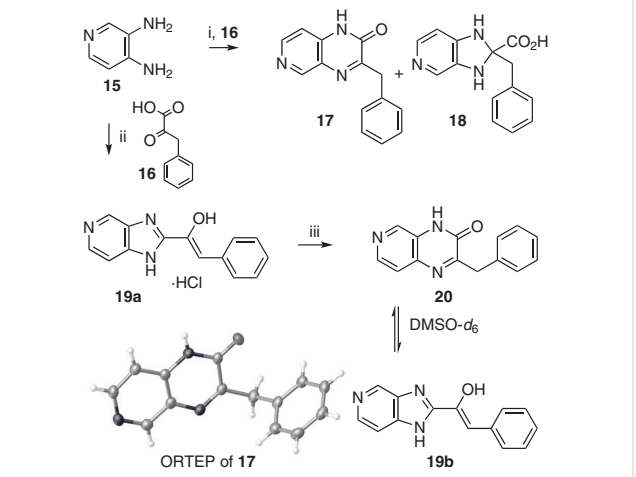


Figure 1 Structures of the compounds **1**–**10** and intermediates **11**–**14**

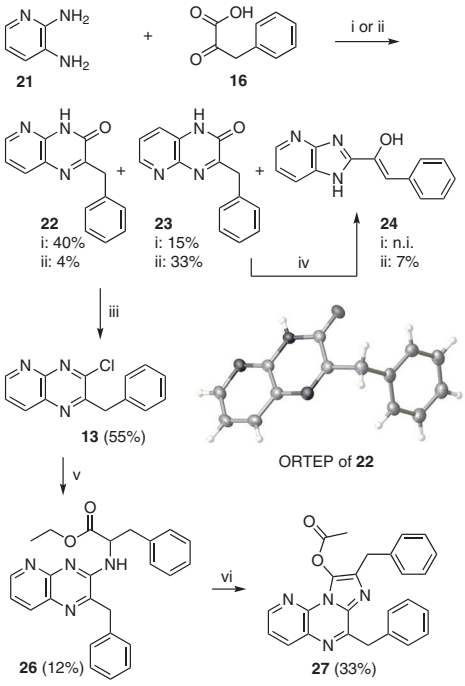
regioselective condensations between 3,4-diaminopyrazine (**15**) and pyruvic acid or ethyl pyruvate in which the acidity of the reaction medium is actually governing the hydration state of the pyruvate and thus the orientation of the reaction.[5] Accordingly, we tried these conditions using phenylpyruvic acid (**16**) instead of pyruvic acid. When heating compounds **15** and **16** in ethanol, the reaction led to the isolation of 34% of the pyrido[3,4-*b*]pyrazin-2-ol **17**, the structure of which was firmly established by means of X-ray diffraction, as depicted here with the corresponding ORTEP representation.

Moreover, a sizable amount of the highly insoluble acid **18** was also obtained, however, this compound could only be partially characterized (by ^{1}H NMR and HRMS) as it turned out to decompose in the course of recrystallization attempts. A drastically different result was obtained when heating compounds **15** and **16** in ethanol along with 3 equivalents of hydrochloric acid (2 N). Indeed, the obtained thick precipitate turned out to be the hydrochloride salt of the imidazopyridine **19a** (featuring a CH signal at 6.74 ppm), which was isolated in an 83% yield and fully characterized. Interestingly, upon basic treatment of this compound, the target isomeric 2-benzylpyrido[3,4-*b*]pyrazin-3-ol (**20**) was then isolated in a 66% yield after a simple extraction. A microanalysis was actually required to confirm this structure since, in solution, the pyridopyrazin-3-ol **20** (characterized by a CH_2 signal at 4.18 ppm and a broad singlet at 12.59 ppm) slowly isomerized into the free base form of imidazopyridine **19b** (displaying a CH signal at 6.45 ppm as well as two broad singlets at 11.05 and 9.50 ppm) and appeared to reach a stable 1:1.6 ratio after 48 hours. To conclude this series of unexpected results, all our attempts to obtain the corresponding chloropyridopyrazines **11** or **12**, from **17** or **20**, using a variety of methods unfortunately failed as extensive decompositions were the sole results. Similarly, methylation trials under basic conditions, or using methyl orthocarboxylates,[6] led to complex mixtures of compounds.

As depicted in Scheme 2, our attempts to prepare the chloropyridopyrazines **13** and **14** were somewhat more successful. Again, a regioselective synthesis of the corresponding 2-benzylpyrido[2,3-*b*]pyrazin-3-ol (**22**) and 3-benzylpyrido[2,3-*b*]pyrazin-2-ol (**23**) relied on the reported mechanistic investigations explaining the orientation of the condensations between 2,3-diaminopyrazine (**21**) and ethyl pyruvate.[5] Of note is that if these reports described rather optimistic yields and selectivity, a subsequent publication using these reagents reported far more sober results.[7] In our case, from 2,3-diaminopyrazine (**21**) and phenylpyruvic acid (**16**), we obtained mixtures of the target isomers **22** and **23** depending on the reaction conditions. Heating the diamine **21** and phenylpyruvic acid (**16**) in ethanol at 85 °C in a closed reactor for 26 hours (conditions i) gave the pyridopyrazine isomers **22** and **23** in 40% and 15% isolated yields, respectively. As depicted in the ORTEP representation, an X-ray diffraction analysis again firmly established the structure of compound **22**. Moreover, the more polar imidazopyridine derivative **24** was also detected in the crude reaction products. Under acidic conditions (conditions ii), the proportion of isomers was inversed and compounds **22** and **23** were isolated in 4% and 33% yields, respectively. Moreover, we could also isolate in this trial 7% of the rather insoluble imidazopyridine derivative **24**. Interestingly, upon treatment of compound **24** with sodium



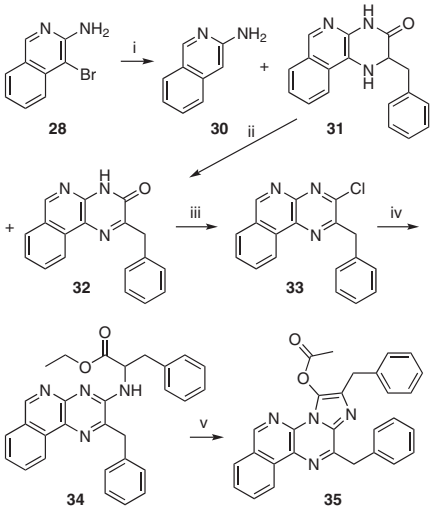
Scheme 1 *Reagents and conditions*: (i) EtOH, reflux; (ii) EtOH, HCl (2 N, 3 equiv); (iii) (1) EtOH, NaOH, reflux, 3 minutes, (2) NH_4Cl.



Scheme 2 *Reagents and conditions*: (i) EtOH, 85 °C; (ii) EtOH, HCl (2 N), reflux; (iii) PCl_3, $POCl_3$, 80 °C; (iv) $POCl_3$ or $PhPOCl_2$ or $SOCl_2$, see text; (v) $PhCH_2CHNH_2CO_2Et$ (**25**), $Pd(OAc)_2$, BINAP, Cs_2CO_3, MeCN, 90 °C; (vi) (1) NaOH, THF, 20 °C, (2) Ac_2O, 20 °C.

hydroxide, and contrary to its isomers **19**, this imidazopyridine mostly underwent extensive decomposition. Chlorination of the hydroxypyridopyrazine isomer **22** was initially problematic, although upon LC/MS monitoring we observed the occurrence of side compounds plausibly arising from oxidation processes. Accordingly, we undertook this reaction in a closed vessel in the presence of phosphorus trichloride as a reducing agent, being very much compatible with the phosphorus oxychloride used for this reaction. This combination proved to be rewarding and we were able to isolate compound **13** in a 55% yield. On the other hand, the use of these conditions, or many others, to obtain the corresponding chlorinated derivative **14** from compound **23** all failed. In every case, the imidazopyridine **24** resulting from a remarkable rearrangement was the sole product detected by ^1H NMR analysis of the reaction (more is suggested regarding this observation in the conclusion). Nevertheless, from the halogenated pyridopyrazine **13** we undertook the preparation of the *O*-acetylated derivative **27**, the stabilized precursor of the target compound **9**. This proceeded via a Buchwald–Hartwig N-arylation of phenylalanine ethyl ester (**25**) to give compound **26** in a rather modest 12% yield. Next, a saponification followed in situ by the addition of an excess of acetic anhydride gave the *O*-acetylated derivative **27** in a 33% yield after chromatography.

As depicted in Scheme 3, we also undertook the preparation of the benzo derivative **35**, which is structurally related to compound **27**. To achieve this, we envisaged a copper chloride catalyzed condensation between the readily available[8] 4-bromoisoquinolin-3-amine (**28**) and phenylalanine (**29**) to give the 1,4-dihydropyrazinoisoquinoline derivative **31**. The first report describing similar transformations mentions the use of 1% of copper chloride, and in most of the examples, the yields described for the corresponding 'dihydro' derivative are quite remarkable.[9] However, in our specific case, we had to resort to the use of 10% of copper chloride to achieve a degree of transformation along with rather low yields. Moreover, we always observed, by LC/MS and ^1H NMR spectroscopy, the occurrence of a sizable amount of the aromatized derivative **32**, which is in accordance with related results described in a later publication.[10] Along with these two compounds, we also noticed the occurrence of the aminoisoquinoline **30**, plausibly resulting from a high temperature DMSO-based reduction process.[11] Eventually, we employed a different set of reported conditions[12] involving copper oxide instead of copper chloride, a somewhat larger excess of the amino acid, a much lower reaction temperature of 90 °C, and an extended reaction time of 40 hours. In our case, from phenylalanine (**29**) and 4-bromoisoquinolin-3-amine (**28**), this led to the expected mixture of the dihydro and the aromatized derivatives **31** and **32** along with some unreacted **28**. As fully detailed below, a procedure was then designed to isolate **31** and **32** from the reaction mixture; treatment of the dihydro derivative **31** with *N*-bromosuccinimide in ethanol, followed by a filtration, gave an additional amount of the aromatized product **32**. With this two-stage procedure an overall yield of 30% of compound **32** was thus achieved

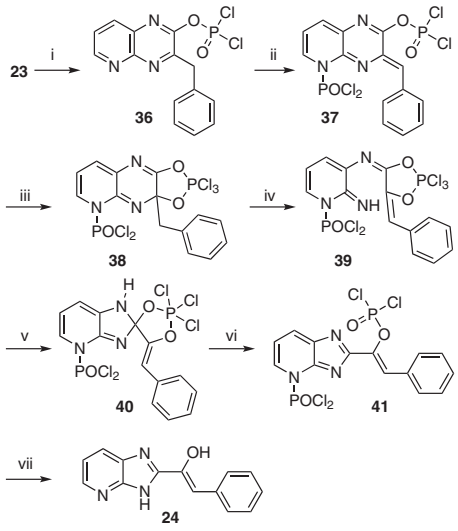


Scheme 3 *Reagents and conditions*: (i) $PhCH_2CHNH_2CO_2H$ (**29**), Cu_2O, K_3PO_4, DMSO, 90 °C; (ii) NBS, EtOH, 20 °C; (iii) PCl_3, $POCl_3$, 80 °C; (iv) $PhCH_2CHNH_2CO_2Et$ (**25**, as a free base), NMP, 120 °C, 4 d; (v) (1) NaOH, THF, 20 °C, (2) Ac_2O, 20 °C.

from compound **28**. Chlorination of compound **32**, using the same combination of PCl_3 and $POCl_3$ mentioned above, then gave the halogenated derivative **33** in 61% yield. The next step turned out to be problematic as the Buchwald–Hartwig N-arylation of phenylalanine ethyl ester (**25**) with compound **33**, using our previously reported conditions,[4] invariably led to extensive decomposition. It was only by heating a solution of the phenylalanine ethyl ester (**25**) (as the free base) and **33** in *N*-methylpyrrolidone (NMP) *without any palladium catalyst* for four days at 120 °C that a degree of N-arylation was achieved and compound **34** was isolated in a 10% yield along with 25% of the starting material **33**. Interestingly, no cyclized product (the target luciferin) could be observed in this step although we previously reported such a reaction in another difficult instance under similar reaction conditions.[1] From this ester, a final step gave the target *O*-acetylated luciferin **35**, albeit in a rather modest 29% yield as chromatography turned out to be necessary.

Unexpectedly and probably because of the inherent basicity of their neighboring nitrogen, the acetyl functionalities of compounds **27** and **35** could not be hydrolyzed under the acidic conditions we had previously used [EtOH, HCl (10 equiv), DMSO at 50 °C for two hours],[4] and even attempts under harsher (acidic) conditions or longer reaction times failed. This problem could be circumvented as the acetyls of compounds **27** and **35** turned out to be readily hydrolyzed in a phosphate buffer (pH 7.4), and as expected, the resulting luciferin immediately reacted with oxygen to decompose and produce a photon. Accordingly, the determination of the chemiluminescence emission spectra of these two analogues was conducted using their *O*-acetylated derivatives immediately after their addition to this buffer at a low (respectively 2.5 μM and 5 μM) final concentration. The use of an Aqualog® (HORIBA Instruments, Inc.), a spectrometer endowed with a sensitive CCD detector (Water-Raman SNR > 20,000:1, RMS method), was again[1] crucial, as was the addition of cetyltrimethylammonium bromide (2.5 mmol) to the buffer which led to a significant enhancement of their signals. As outlined in the experimental section, the λ_{max} values measured for the chemiluminescence of compounds **27** and **35** were 546 nm and 462 nm, respectively.

In conclusion, our attempts to prepare the four possible aza-analogues of luciferin **2a** met with quite a lot of unexpected problems. If the preparation and isolation of the benzylpyridopyrazinol precursors **17**, **20**, **22** and **23** could be achieved in rather modest yields, their transformation into the four corresponding halogenated derivatives turned out to be possible in only one instance. The rather unexpected rearrangement of compound **23** into the imidazopyridine **24** upon treatment with reagents such as $POCl_3$ or $SOCl_2$ actually provides some insights into the reactivity of such heterocyclic systems and is actually reminiscent of various previously reported quinoxalinone ring contractions into benzimidazoles.[13] In our case, we suggest the mechanism depicted in Scheme 4 to account for this experimental observation.



Scheme 4 Suggested mechanism for the rearrangement of **23** into **24**. *Reagents and conditions*: (i) first addition of $POCl_3$, (– HCl); (ii) second addition of $POCl_3$, (– HCl); (iii) cyclization (+ HCl); (iv) and (v) rearrangement of the carbon–nitrogen bond; (vi) HCl elimination; (vii) hydrolysis (upon treatment) of the two phosphoryl dichlorides.

The depicted second addition of phosphorus oxychloride [step (ii)] on the nitrogen of compound **23** to give intermediate **37** could be the key accounting for the fragility of the pyrazine ring and its contraction into the imidazole component of compound **24** via penta-coordinated phosphorus-containing intermediates **38**–**40**. A similar process can also be written with thionyl chloride leading to a tetracoordinated sulfur intermediate.

Of note in this work is the use of the inherently reductive mixture of phosphorus oxychloride and phosphorus trichloride to achieve the preparation of compounds **13** and **33**. We are not aware of any reports describing the advantages of using such reaction conditions. Concerning the chemiluminescence study, even if the two prepared *O*-acetylated proluciferin analogues **27** and **35** could not be hydrolyzed under acidic conditions, we were able to determine their emission spectra by adding them to a neutral phosphate buffer, which led in situ to the hydrolysis of their acetyl moiety. Interestingly, from compound **27**, the luciferin **9** turned out be endowed with yellow-colored chemiluminescence spectra (λ_{max} of 546 nm), being even better than the green-emitting compound **2b** (λ_{max} = 513 nm). On the other hand, in the same phosphate buffer, the benzo derivative **35** gave a blue signal at 462 nm, thus negating any gain from the insertion of the nitrogen in this heterocyclic system. In conclusion, the shift in emission observed from the *O*-acetylated analogue **27** is encouraging, although the chemistry to generate further derivatives will need to

address the difficulties described in this report. In any case, the determined λ_{max} experimental values should again[4] be useful for the design and validation of computer-based models[14] of such light-producing decarboxylation reactions.

When specified, the anhydrous solvents used were purchased. Experiments under inert atmospheres were carried out by purging the glassware with a stream of dry argon. Then, an argon balloon, fitted with a needle, was used to insure a positive pressure of inert gas during the reaction. Column chromatography was performed either on Merck silica gel 60 (0.035–0.070 mm) or on neutral alumina containing 1.5% of added water using a solvent pump and an automated collecting system driven by a UV detector set to 254 nm, unless required otherwise. Sample deposition was carried out by absorption of the mixture to be purified on a small amount of the solid phase followed by its deposition on the top of the column. Unless stated otherwise, a purity of at least 95% was obtained for all the compounds by means of chromatography or recrystallization, and this level of purity was established by TLC, LC/MS and NMR spectroscopy.

The X-ray-based structural elucidation of compounds **17** (CCDC 2056217) and **22** (CCDC 2056386) was achieved using the beamline PROXIMA-2 at Synchrotron SOLEIL. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, respectively. Chemical shifts (δ) are given in ppm with respect to the TMS signal and cross-coupling constants (*J*) are given in hertz. Low-resolution mass spectra were obtained on an Agilent 1100 series LC/MSD system using an atmospheric electrospray ionization system or an Agilent 1200 series LC/MSD system employing an Agilent Jet-Stream atmospheric electrospray ionization system. High-resolution mass spectrometry (HRMS) was performed using a Waters Micromass Q-Tof with an electrospray ion source. Elemental analysis were performed by the Service de Microanalyse de l'ICSN, CNRS, Gif sur Yvette, France.

The time-dependent chemiluminescence signals were recorded using an Aqualog (HORIBA Instruments, Inc.) equipped with a thermoelectrically cooled charge-coupled device (CCD) array detector. The system uses a xenon arc light source to excite samples and two detectors for simultaneous absorbance, transmission and emission analysis was adapted to the chemiluminescence analysis by blocking the excitation source. The 2D emission spectra were recorded from 250 to 800 nm using 5 nm steps, high gain and 30 s integration times for emission detection. A detector accumulation of 2 was chosen to improve the signal-to-noise ratio and increase the photon counts. Chemiluminescence data were corrected for the instrumental emission spectral response, detector dark currents and blank sample emission. All samples were analyzed using fluorescence quartz cuvettes (1 cm path length), and the signal was recorded immediately after addition of either 1 or 2 µL of a 5 mM stock solution in DMSO of the *O*-acetylated luciferin in 2 mL of the phosphate buffer DPBS GIBCO 1X, which also contained 2.5 mM of cetyltrimethylammonium bromide. The chemiluminescence data were analyzed using Aqualog software based on OriginLab® and the signal was smoothed by 4 points fast Fourier transform (FFT).

Condensation of 3,4-Diaminopyrazine (15) and Phenylpyruvic Acid (16) under Neutral Conditions

In a 60 mL tube fitted with a Teflon-covered screw cap, 3,4-diaminopyrazine (**15**) (1.82 g, 16.67 mmol) and phenylpyruvic acid (**16**) (2.73 g, 16.67 mmol) were dispersed in ethanol (40 mL, dried over 4 Å molecular sieves). The tube was closed tightly and heated at 85 °C for 24 hours. The resulting suspension was dispersed in boiling ethanol (100 mL), left to cool and filtered, and this material was subjected again to this treatment to give, after drying, compound **18** (0.98 g) as a white powder which could not be further purified, probably because of the onset of an oxidative decarboxylation characterized by the appearance in LC/MS of a compound with a mass of *m*/*z* = 210. Both filtrates were collected, concentrated to dryness and purified by chromatography over silica gel (dichloromethane/ethanol, 97:3 to 94:6) to yield compound **17** (1.37 g, 34%) as a white powder after dispersion of the corresponding fraction in boiling ethanol (100 mL) and filtration following cooling.

3-Benzylpyrido[3,4-*b*]pyrazin-2-ol (17)

Note: the structure of this compound (recrystallized in ethanol) was further established by X-ray crystallography.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.61 (br s, 1 H), 8.86 (br s, 1 H), 8.45 (d, *J* = 5.5 Hz, 1 H), 7.35–7.27 (m, 3 H), 7.23–7.18 (m, 2 H), 4.14 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.8, 155.3, 150.2, 149.0, 137.9, 137.4, 129.7, 128.8, 128.6, 126.9, 39.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{12}N_3O$: 238.0980; found: 238.0975.

2-Benzyl-2,3-dihydro-1*H*-imidazo[4,5-*c*]pyridine-2-carboxylic Acid (18)

^{1}H NMR (400 MHz, DMSO-d_6, still containing some EtOH): δ = 9.20 (br s, 1 H), 7.48 (d, *J* = 6.1 Hz, 1 H), 7.23–7.21 (m, 2 H), 7.18–7.09 (m, 3 H), 6.96 (s, 1 H), 6.89 (br s, 1 H), 6.17 (d, *J* = 6.2 Hz 1 H), 3.03 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): not soluble enough.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}N_3O_2$: 256.1086; found: 256.1081.

Note: the growing occurrence of another compound (*m*/*z* = 210 and, amongst others, a singlet ^{1}H signal at 4.23 ppm) was noticed when trying to further purify this batch using a third dispersion.

1-(1*H*-Imidazo[4,5-*c*]pyridin-2-yl)-2-phenylethen-1-ol Hydrochloride Salt (19a)

A mixture of 3,4-diaminopyrazine (**15**) (2.26 g, 20.70 mmol), phenylpyruvic acid (**16**) (3.39 g, 20.70 mmol), ethanol (40 mL) and 2 N hydrochloric acid (31 mL, 62.12 mmol) was heated to reflux for 2 h. This was left to cool and the resulting precipitate was filtered off, washed with ethanol and dried under vacuum at 60 °C to yield pure compound **19a** (4.75 g, 83%) as the hydrochloride salt.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 14.40 (br s, 1 H), 11.62 (s, 1 H), 10.72 (br s, 1 H), 8.15 (dd, *J* = 6.6, 1.0 Hz, 1 H), 8.03 (d, *J* = 1.0 Hz, 1 H), 7.56 (m, 2 H), 7.47 (m, 2 H), 7.41 (d, *J* = 6.6 Hz, 1 H), 7.36 (m, 1 H), 6.74 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.6, 141.6, 136.1, 133.8, 129.3 (two signals), 128.4, 127.0, 125.0, 124.6, 111.5, 109.1.

HRMS (ESI): *m*/*z* [M + H – HCl]$^+$ calcd for $C_{14}H_{12}N_3O$: 238.0980; found: 238.0985.

Anal. Calcd for $C_{14}H_{11}N_3O$ + HCl: C, 61.43; H, 4.42; N, 15.35; O, 5.85. Found: C, 61.23; H, 4.42; N, 15.41; O, 6.14.

2-Benzylpyrido[3,4-*b*]pyrazin-3-ol (20)

Compound **19a** (0.19 g, 0.69 mmol) and sodium hydroxide (0.2 g, 5 mmol) were brought to reflux in ethanol/water (1:1, 20 mL). This was left to cool, neutralized with solid ammonium chloride diluted in water and extracted with ethyl acetate (2 × 50 mL). The organic layer was washed with brine (25 mL), dried over magnesium sulfate and concentrated to dryness to yield pure compound **20** (0.11 g, 66%) as a beige powder. If ^{1}H and ^{13}C NMR analysis were run using a freshly made sample of compound **20**, the following spectra were obtained:

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.59 (br s, 1 H), 8.63 (d, *J* = 0.6 Hz, 1 H), 8.40 (d, *J* = 5.3 Hz, 1 H), 7.65 (dd, *J* = 5.3, 0.6 Hz, 1 H), 7.34–7.27 (m, 4 H), 7.22 (m, 1 H), 4.18 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.0, 154.6, 143.9, 139.1, 137.1, 135.7, 129.8, 128.8, 128.5, 127.0, 121.5, 39.7.

Following about 24 hours in the DMSO-d_6 solution, the occurrence of a second product could be seen and subtraction of the signals described above gave the following spectra compatible with the free base form of compound **19**:

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.05 (br s, 1 H), 9.50 (br s, 1 H), 7.99 (s, 1 H), 7.92 (d, *J* = 5.5 Hz, 1 H), 7.52 (d, *J* = 7.9 Hz, 2 H), 7.43–7.39 (m, 2 H), 7.28–7.25 (m, 1 H), 7.06 (d, *J* = 5.5 Hz, 1 H), 6.44 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.8, 144.5, 135.6, 135.2, 134.6, 129.2, 129.0, 128.7, 127.1, 122.8, 108.6, 105.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{12}N_3O$: 238.0980; found: 238.0983.

Note: when using formic acid as the vector, a peak at *m*/*z* = 256.1074 was also present.

Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71; O, 6.74. Found: C, 70.39; H, 4.81; N, 17.63; O, 6.77.

Condensation of 2,3-Diaminopyrazine (21) and Phenylpyruvic Acid (16) under Neutral Conditions

In a 60 mL tube fitted with a Teflon-covered screw cap, 1,2-diaminobenzene (**21**) (1.39 g, 12.73 mmol) and phenylpyruvic acid (**16**) (2.09 g, 12.73 mmol) were heated at 85 °C in ethanol (25 mL) for 26 hours. The resulting solution was concentrated to dryness and the residue purified by chromatography over silica gel (dichloromethane/ethanol, 98:2 to 96:4) to give, in that order of elution, compound **22** (1.21 g, 40%) and its isomer **23** (0.48 g, 15%) as described below.

Condensation of 2,3-Diaminopyrazine (21) and Phenylpyruvic Acid (16) under Acidic Conditions

A mixture of 1,2-diaminobenzene (**21**) (1.32 g, 12.10 mmol), phenylpyruvic acid (**16**) (2.00 g, 12.10 mmol), and 2 N hydrochloric acid (18.1 mL, 36.29 mmol) was heated to reflux in ethanol (20 mL) for 26 hours. The resulting solution was cooled, diluted with water (100 mL), and made basic with solid sodium hydrogen carbonate. The resulting precipitate was filtered off and the filtrate was extracted with ethyl acetate (2 × 50 mL). The organic layer was washed with water (30 mL) and brine (30 mL), dried over magnesium sulfate and concentrated to dryness. This residue and the precipitate described above were both adsorbed on silica gel and purified by chromatography over silica gel (dichloromethane/ethanol, 98:2) to give an unclean fraction containing compound **22** (0.25 g) and then a clean fraction of compound **23** (0.95 g, 33%). Further purification of the first fraction by a second chromatography over silica gel (cyclohexane/ethyl acetate, 2:1 to 1:0) gave pure compound **22** (0.11 g, 4%). In another trial, extensive dispersion of the initial precipitate in ethyl acetate (100 mL) and water (100 mL) followed by filtration of the remaining insoluble material gave a solid which was purified by chromatography over silica gel (dichloromethane/ethanol, 97:3) to give a fraction (0.98 g) containing the imidazo[4,5-*b*]pyridine **24**. This was further purified by dispersion in boiling ethanol (40 mL) to give a pure sample of **24** (0.32 g, 7%) as described below.

2-Benzylpyrido[2,3-*b*]pyrazin-3-ol (22)

Note: as described above, the structure of this compound (recrystallized in ethanol) was further established by X-ray crystallography. In addition, the ^{1}H spectrum was similar to the substance obtained using a different (but plausibly acid-containing) synthetic approach, which gave very optimistic yields that we could not reproduce.[15]

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.84 (br s, 1 H), 8.48 (dd, *J* = 4.7, 1.7 Hz, 1 H), 8.14 (dd, *J* = 7.8, 1.7 Hz, 1 H), 7.37–7.27 (m, 5 H), 7.22 (m, 1 H), 4.15 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.1, 156.3, 150.1, 144.3, 137.5, 136.7, 129.7, 128.8, 127.3, 126.9, 102.1, 39.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{11}N_3ONa$: 260.0800; found: 260.0805.

3-Benzylpyrido[2,3-*b*]pyrazin-2-ol (23)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.51 (br s, 1 H), 8.48 (dd, *J* = 4.5, 1.7 Hz, 1 H), 7.69 (dd, *J* = 8.2, 1.7 Hz, 1 H), 7.51 (dd, *J* = 8.1, 4.5 Hz, 1 H), 7.37–7.20 (m, 5 H), 4.18 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.7, 154.6, 145.3, 143.0, 137.4, 129.8, 128.8, 128.3, 126.9, 125.2, 124.6, 39.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{12}N_3O$: 238.0980; found: 238.0971.

1-(1*H*-Imidazo[4,5-*b*]pyridin-2-yl)-2-phenylethen-1-ol (24)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.06 (br s, 1 H), 9.20 (br s, 1 H), 7.80 (dd, *J* = 4.9, 1.4 Hz, 1 H), 7.55 (m, 2 H), 7.39 (m, 2 H), 7.24 (m, 1 H), 7.16 (dd, *J* = 7.7, 1.4 Hz, 1 H), 6.80 (dd, *J* = 7.7, 4.9 Hz, 1 H), 6.41 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.6, 141.6, 135.4, 129.8, 129.3, 129.2, 128.5, 127.0, 121.5, 121.1, 116.3, 105.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{12}N_3O$: 238.0980; found: 238.0969.

2-Benzyl-3-chloropyrido[2,3-*b*]pyrazine (13)

In a 60 mL tube fitted with a Teflon-covered screw cap, compound **23** (0.4 g, 1.68 mmol) was dispersed in a mixture of phosphorus oxychloride (4 mL) and phosphorus trichloride (2 mL). The tube was closed and heated at 80 °C in an oil bath for 40 minutes. The resulting solution was diluted in ethyl acetate (100 mL), poured onto an excess of ice and stirred for 15 minutes. The organic layer was made basic with 1 N ammonia, washed with water (30 mL) and brine (30 mL), dried over magnesium sulfate and concentrated to dryness. The residue was purified by chromatography over silica gel (cyclohexane/ethyl acetate, 3:1) to give compound **13** (0.35 g, 81%) as a white solid. Note: as mentioned in scheme 2, a 55% yield was obtained when running the reaction on 0.15 g of compound **23** and heating 12h.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.13 (dd, *J* = 4.2, 1.9 Hz, 1 H), 7.73 (dd, *J* = 8.3, 4.2 Hz, 1 H), 7.73 (dd, *J* = 8.3, 1.9 Hz, 1 H), 7.34 (m, 5 H), 4.57 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 154.1, 150.6, 149.4, 137.9, 136.2, 136.1, 129.2, 128.6, 127.0, 125.4, 41.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{11}N_3Cl$: 256.0641; found: 256.0634.

Ethyl (2-Benzylpyrido[2,3-*b*]pyrazin-3-yl)phenylalaninate (26)

To a 20 mL sealable vial fitted with a septum were added compound **13** (0.31 g, 1.21 mmol), phenylalanine ethyl ester hydrochloride salt (**25**) (0.28 g, 1.21 mmol), cesium carbonate (1.3 g, 3.87 mmol), palladium diacetate (0.013 g, 0.06 mmol) and BINAP (0.053 g, 0.084 mmol). The air was replaced by argon and, under an inert atmosphere, dry acetonitrile (4 mL) was added via syringe. The mixture was stirred and heated at 60 °C for 12 hours. The resulting suspension was diluted in ethyl acetate (75 mL), filtered, the filtrate was concentrated to dryness and the residue purified by chromatography over silica gel (cyclohexane/ethyl acetate, 2:1) to give compound **26** (0.06 g, 12%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.86 (dd, *J* = 4.5, 2.0 Hz, 1 H), 8.25 (dd, *J* = 8.1, 2.0 Hz, 1 H), 7.38 (dd, *J* = 8.1, 4.5 Hz, 1 H), 7.29 (m, 3 H), 7.20–7.14 (m, 5 H), 6.89 (m, 2 H), 5.64 (d, *J* = 7.4 Hz, 1 H), 5.38 (m, 1 H), 4.24 (s, 2 H), 4.14 (m, 2 H), 3.34 (dd, *J* = 14.2, 5.4 Hz, 1 H), 3.17 (dd, *J* = 14.2, 5.2 Hz, 1 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6, 152.0, 151.5, 151.0, 147.7, 137.2, 135.9, 135.0, 131.4, 129.3, 129.1, 128.6, 127.4, 126.8, 120.4, 61.5, 54.3, 41.3, 37.1, 14.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{25}N_4O_2$: 413.1978; found: 413.1980.

6,8-Dibenzylimidazo[1,2-*a*]pyrido[3,2-*e*]pyrazin-9-yl Acetate (27)

Compound **26** (0.06 g, 0.14 mmol) and powdered sodium hydroxide (0.023 g, 0.58 mmol) were added to a 100 mL flask. The air was replaced by argon and dry THF (0.2 mL) was added via syringe. The mixture was stirred for 19 hours and acetic anhydride (0.2 mL, 2.18 mmol) was then added via syringe. The resulting suspension was stirred for 2 hours, diluted in water, stirred for 15 minutes and extracted with ethyl acetate (2 × 50 mL). The organic layer was washed with water (30 mL) and brine (30 mL), dried over magnesium sulfate and concentrated to dryness. The residue was purified by chromatography over silica gel (cyclohexane/ethyl acetate, 4:1) to give compound **27** (0.02 g, 33%) as a pale pink glass.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (dd, *J* = 4.7, 1.7 Hz, 1 H), 8.31 (dd, *J* = 8.2, 1.7 Hz, 1 H), 7.60 (m, 2 H), 7.47 (dd, *J* = 8.2, 4.7 Hz, 1 H), 7.38–7.18 (m, 8 H), 4.63 (s, 2 H), 4.22 (s, 2 H), 2.39 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 155.4, 146.9, 139.5, 138.4, 137.4, 137.3, 134.5, 134.4, 131.9, 131.1, 129.8, 129.0, 128.4, 128.3, 126.6, 126.4, 122.1, 39.6, 33.1, 20.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{21}N_4O_2$: 409.1664; found: 409.1667.

4-Bromoisoquinolin-3-amine (28)

The procedure described on page 67 of a patent[8] was followed and compound **28** (7.09 g, 87%) was obtained as a yellow powder after a purification by chromatography over silica gel (cyclohexane/ethyl acetate, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.81 (s, 1 H), 7.93 (m, 1 H), 7.81 (m, 1 H), 7.67 (m, 1 H), 7.34 (m, 1 H), 5.03 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.7, 150.5, 137.0, 131.9, 128.1, 124.8, 123.8, 123.6, 97.6.

2-Benzylpyrazino[2,3-*c*]isoquinolin-3-ol (32)

To a 60 mL tube fitted with a Teflon-covered screw cap were added compound **28** (1.61 g, 7.21 mmol), racemic phenylalanine (**29**) (3.6 g, 21.6 mmol), potassium phosphate (4.6 g, 7.21 mmol) and copper(I) oxide (0.05 g, 0.36 mmol). Dry DMSO (15 mL) was added, the tube closed and the contents heated using an oil bath at 90 °C for 40 hours. The resulting orange suspension was dispersed in a mixture of water (100 mL), ethyl acetate (50 mL), ammonium chloride (1.1 g) and 30% ammonia (10 mL) and stirred in open air for 30 minutes. The resulting precipitate was filtered, washed with water (2 × 50 mL) and ethyl acetate (2 × 50 mL) and then dried under vacuum at 50 °C to give pure compound **32** (0.38 g, 18%) as a white powder. The filtrate was extracted with ethyl acetate (2 × 50 mL). The organic layer was washed with water (30 mL) and brine (30 mL), dried over magnesium sulfate and concentrated to dryness. Chromatography over silica gel (cyclohexane/ethyl acetate, 2:1) of the resulting residue gave an impure fraction containing the dihydro derivative **31** (0.47 g). This was dispersed in ethanol, *N*-bromosuccinimide was added (0.43 g) and the suspension was stirred for 90 minutes. The resulting precipitate was filtered, washed with ethanol and dried under vacuum at 50 °C to give additional compound **32** (0.26 g, 12%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.1 (s, 1 H), 9.29 (s, 1 H), 8.60 (m, 1 H), 8.20 (m, 1 H), 7.93 (m, 1 H), 7.68 (m, 1 H), 7.41 (m, 2 H), 7.32 (m, 2 H), 7.23 (m, 1 H), 4.25 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.2, 156.5, 154.5, 139.7, 137.8, 133.3, 132.7, 129.8, 128.8, 128.7, 126.9, 126.8, 126.4, 121.4, 119.9, 39.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}N_3O$: 288.1137; found: 288.1136.

2-Benzyl-3-chloropyrazino[2,3-*c*]isoquinoline (33)

In a 60 mL tube fitted with a Teflon-covered screw cap, compound **32** (1.4 g, 4.59 mmol) was dispersed in a mixture of phosphorus oxychloride (10 mL) and phosphorus trichloride (5 mL). The tube was closed and heated at 120 °C in an oil bath for 23 hours. The resulting solution was diluted in ethyl acetate (100 mL), poured onto an excess of ice and stirred for 15 minutes. The organic layer was made basic with 1 N ammonia, washed with water (2 × 30 mL) and brine (30 mL), dried over magnesium sulfate and concentrated to dryness. The residue was purified by chromatography over silica gel (cyclohexane/ethyl acetate, 4:1) to give compound **33** (0.90 g, 61%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.55 (s, 1 H), 9.11 (m, 1 H), 8.17 (m, 1 H), 8.02 (m, 1 H), 7.91 (m, 1 H), 7.44 (m, 2 H), 7.34 (m, 2 H), 7.26 (m, 1 H), 4.64 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 154.0, 148.4, 146.5, 136.7, 133.7, 133.2, 132.2, 129.9, 129.3, 128.6, 128.5, 128.2, 126.9, 123.8, 41.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{13}ClN_3$: 306.0798; found: 306.0793.

Ethyl (2-Benzylpyrazino[2,3-*c*]isoquinolin-3-yl)phenylalaninate (34)

In a 60 mL tube fitted with a Teflon-covered screw cap, compound **33** (0.43 g, 1.41 mmol) and freshly extracted phenylalanine ethyl ester (**25**) (0.55 g, 2.81 mmol) were dissolved in dry *N*-methylpyrrolidone (4 mL). The tube was closed and heated using an oil bath at 120 °C for four days. The resulting black solution was diluted in saturated sodium hydrogen carbonate (150 mL) and was extracted with ethyl acetate (2 × 50 mL). The organic layer was washed with water (30 mL) and brine (30 mL), dried over magnesium sulfate and concentrated to

dryness. The residue was purified by a chromatography over silica gel (cyclohexane/ethyl acetate, 3:1) to give compound **34** (0.14 g, 10%) as an oil. In another chromatographic fraction, pure starting material **33** (0.14 g, 25%) was recovered.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.40 (s, 1 H), 9.00 (m, 1 H), 8.05 (m, 1 H), 7.88 (m, 1 H), 7.69 (m, 1 H), 7.28 (m, 5 H), 7.19 (m, 3 H), 6.94 (m, 2 H), 5.46 (m, 2 H), 4.33 (s, 2 H), 4.17 (m, 2 H), 3.38 (dd, *J* = 14.0, 4.9 Hz 1 H), 3.22 (dd, *J* = 14.0, 5.3 Hz, 1 H), 1.24 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 155.8, 151.2, 147.2, 144.6, 136.2, 135.8, 134.3, 131.3, 129.4, 129.0, 128.7, 128.6, 128.4, 127.9, 127.2, 127.0, 126.8, 126.7, 122.3, 61.4, 54.4, 41.1, 37.4, 14.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{27}N_4O_2$: 463.2129; found: 463.2124.

2,12-Dibenzylimidazo[1′,2′:1,6]pyrazino[2,3-*c*]isoquinolin-3-yl Acetate (35)

Compound **34** (0.14 g, 0.30 mmol) and powdered sodium hydroxide (0.05 g, 1.2 mmol) were added to a 100 mL flask. The air was replaced by argon and dry THF (3 mL) was added via syringe. The mixture was stirred for 19 hours and acetic anhydride (0.43 mL, 4.51 mmol) was then added via syringe. The resulting suspension was stirred for 2 hours, diluted in water (50 mL), stirred for 15 minutes and extracted with ethyl acetate (2 × 50 mL). The organic layer was washed with water (30 mL) and brine (30 mL), dried over magnesium sulfate and concentrated to dryness. The residue was purified by chromatography over silica gel (cyclohexane/ethyl acetate, 6:1) to give compound **35** (0.04 g, 29%) as a beige solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.07 (s, 1 H) 9.04–9.02 (m, 1 H), 8.01–7.99 (m, 1 H), 7.87 (m, 1 H), 7.67 (m, 3 H), 7.41 (m, 2 H), 7.35 (m, 4 H), 7.26 (m, 2 H), 4.75 (s, 2 H), 4.28 (s, 2 H), 2.42 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 153.3, 150.3, 138.5, 137.7, 134.9, 134.8, 134.1, 134.0, 131.5, 131.4, 129.9, 129.0, 128.4, 128.3, 127.5, 127.4, 126.5, 126.3, 125.4, 123.5, 39.5, 33.4, 20.5 (one signal missing).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{23}N_4O_2$: 459.1821; found: 459.1822.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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